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10/581,911	06/07/2006	Naoko Kida	Q95279	8940

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EXAMINER	
UNDERDAHL, THANE E	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/581,911	KIDA ET AL.	
	Examiner	Art Unit	
	THANE UNDERDAHL	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7 and 9-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-7, 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This Office Action is in response to the Applicant's reply received 7/24/09. Claims 1-3, 5-7, 9-11 are pending. No Claims are withdrawn. Claims 4 and 8 are cancelled. Claim 1 has been amended. No Claims are new. Claims 1-3, 5-7, 9-11 are considered in this Office Action.

Response to Claim Amendments and Arguments

In the response submitted by the Applicant the following 35 U.S.C § 103 (a) rejections are withdrawn:

- Claims 1-3, 5, 6, 9-11 as being unpatentable over Goodwin #1, Goodwin #2, Goodwin #3 and Schwarz et al. in light of support from Unsworth et al., Wikipedia, Bock et al. and Bartlett.
- Claims 1-3, 5-7, and 9-11 as being unpatentable over Goodwin #1, #2, #3 and Schwarz et al. in light of various supporting references as applied to claims 1-3, 5, 6, 9-11 above, and further in view of Yan et al. and Simpson et al.

The Applicant's amendments limiting the cells to mesenchymal stem cells and that step (b) occurs with no carrier necessitated the above withdrawal.

New Rejections Necessitated By Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-7, 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some "inducers of cartilage differentiation"

such as TFG-β or dexamethasone, does not reasonably provide enablement for every possible compound that can induce cartilage differentiation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to perform the invention commensurate in scope with these claims.

The written description requirement is in place to ensure that "when a patent claims a genus by its function or result, the specification recites sufficient materials to accomplish that function." *Ariad Pharms. Co. v. Eli Lilly & Co.*, 94 U.S.P.Q.2d 1161, 1172 (Fed. Cir. 2010) (en banc). A consideration of the four corners of the specification does not reflect that applicants have actually invented the claimed invention, since the Applicant has shown only two inducers of cartilage differentiation. The specification does not permit the skilled artisan to visualize all of the members of the genus “cartilage inducers” being administered in the claimed methods.

If claims merely recite a "description of the problem to be solved while claiming all solutions to it" and the claim scope "cover any compound later actually invented and determined to fall within the claim’s functional boundaries," they have not met the description requirement. *Ariad*, 94 U.S.P.Q.2d at 1172. Such is the case here, especially given the fact that applicants’ disclosure contains only a prophetic example of the claimed method, i.e. "a mere mention of a desired outcome." *Id.* at 1176. Applicant might overcome this rejection by establishing that the art recognizes a correlation between the structure of the “inducer of cartilage differentiation” administered in the claim and their function. *Id.* at 1171.

Applicants' disclosure appears to be an investigation of a mechanism of how cartilage differentiation is induced. However, "[p]atents are not awarded for academic theories, no matter how groundbreaking or necessary to the later patentable inventions of others." *Ariad*, 94 U.S.P.Q.2d at 1173. The patent system is designed to give incentives for innovators to complete inventions, not to guess at the future. *Id.* at 1174.

Furthermore the new limitation "culturing cells of step (b) without a carrier" is not enabled for the entire scope since "carrier" defined broadly by one of ordinary skill in the art can include liquid culture media or pharmaceutical carriers such as water as well as common cell culture scaffolds or beads that cells adhere. Cleary the specification does not teach a scenario that excludes culture media or other liquids commonly thought necessary by one of ordinary skill in the art for in-vitro cell culture.

Claims 1-3, 6-7, 9-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Applicant claims that the cells used in the method of claim 1 are "bone marrow mesenchymal stem cells". The Applicant supports this by citing the art of Maniatopoulos et al. (Cell Tissue Res, vol 254, pages 317-330 1988) was used to isolate these cells (Specification, pg 9, Example 1). However upon review of this article it is not clear if indeed Maniatopoulos et al.describes such cells. Maniatopoulos et al.aspirates the whole bone marrow of rat femurs and then cultures the entire marrow *in vitro* using common laboratory cell culture techniques. There is no

evidence presented by Maniatopoulos et al. that typical stem cell characteristics exist in their cells cultured from the entire bone marrow. These characteristics include self-renewal, pluropotency, and common markers such as CD34+, BMPR, Sca-1, SCF, AFP etc. Therefore it is unclear to the Examiner if the Applicant had possession of mesenchymal stem cells or a collection of cells located inside the bone marrow.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6-7, 9-11 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 includes the new limitation that the cells are “in the presence of an inducer of cartilage differentiation”. This is indefinite since it is not clear if "in the presence of" limits that the cartilage inducer is in the same solution or stored in a bottle next to the rotary bioreactor. Clarification is required.

Also it is clear in the specification that TGF-beta and dexamethasone are cartilage inducers but it is not clear in the dependant claim 7 that these compounds further limit cartilage inducers or that they are simply components further comprised in the culture media. Clarification is required.

The phrase “in a simulated microgravity environment with the use of a uniaxial rotary bioreactor that realizes a simulated microgravity environment on earth” is indefinite. It is unclear if the “uniaxial rotary bioreactor” is actually producing a

“simulated microgravity environment”. The claim would be more definite if phrased "(c) three-dimensionally culturing the cells of step (b) without a carrier in a uniaxial rotary bioreactor that simulates a microgravity environment on earth by compensating the ground gravity with the stress resulting from controlled rotation speed”. While continuing to be a Product-by-process limitation, this limitation clearly indicates that the bioreactor is directly responsible for producing a microgravity environment.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the method steps used in "obtaining cartilage tissue expressing Type II collagen". It is unclear if this cartilage is isolated or separated from the cells.

Claim 6 and 9 are indefinite since the limitations of “bone marrow cells” or “bone marrow mesenchymal cells” do not have antecedent basis. Also claims 6 and 9 are indefinite because they do not further limit the cells of claim 1 since "bone marrow cells" and “bone marrow mesenchymal cells” are broader in scope than then "bone marrow mesenchymal stem cells" of claim 1. The Examiner suggests replacing “bone marrow cells” and “bone marrow mesenchymal cells” with "bone marrow mesenchymal stem cells" as limited in claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zayzafoon et al. (Endocrinology, 2004), Ito et al. (PTO 1449, 10/13/09, #V) and in further view of Duke et al. (Adv Space Res, 1996) in light of support by Unsworth et al. (PTO 1449, 5/1/07 #U), Ito et al. (PTO 1449, 10/13/09, #U), Wexler et al.(British Journal of Haemotoltogy 2003) and further support of Schwartz (PTO 1449, 5/1/07 #D).

Claim 1 part (d) is an intended result that is not given significant patentable weight in this method claim. The limitation that type II collagen tissue is obtained is an intended result and not an active step of the method. Any art disclosing the same steps as the proposed method will either inherently meet this limitation or obviously meet this limitation. Also claim 10 is an intended result of the method since it limits that the cartilage tissue has a major axis of 1 cm or more. It would be inherent that art reading on the same method steps would achieve the same results and therefore would meet this limitation.

Zayzafoon et al. teach that **mesenchymal stem cells** (**MSC**) are cultured two-dimensionally in T-175 flasks then detached with trypsin and EDTA to be seeded on microcarriers and cultured in a **rotary wall vessel** (**RWV**) bioreactor (Zayazfoon, pg 2422, col 2, Materials and Methods). It is known in the art that RWV reactors can simulate an environment of 10^{-2} (1/100 th) of ground gravity by controlling its rotational speed as supported by Unsworth et al.(Unsworth et al., page 902, col 1). Schwarz et al.

shows that one of ordinary skill in the art can controlled rotation of an RWV between 5 and 40 RPM (Schwarz, col 7, lines 5-10). Schwarz et al. teach that the rotation speed is increased and decreased to synchronize the falling cells with the rotating reactor so the cells are maintained floating in suspension (i.e. defy gravity) (Schwarz, Claim 3). Zayzafoon et al. teach that dexamethasone is added to the media (pg 2423, col 1, top). While Zayazfoon et al. teach that their MSCs are cultured to subconfluence (Zayazfoon, pg 2422, col 2, last paragraph) one of ordinary skill in the art would recognize that this is a variable that can be routinely optimized. Indeed this is supported by art of Ito et al. or Wexler et al. that teach that MSCs can be cultured confluence (Ito, pg 120, col 2, top and Wexler pg 369, col 1 Materials and Methods). Therefore it would be obvious for one of ordinary skill in the art to meet the claim limitations and culture the MSCs to confluence since this is an accepted range presented in the art to culture MSCs for experimentation (MPEP 2144.05 II). Also while Zayazfoon et al. does not teach the concentration of cells seeded into the RVW seen in claim 6. However, M.P.E.P. § 2144.05 II states:

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical.

Absent any teaching of criticality by the applicant concerning the cell concentrations listed in claim 6, it would be *prima facie* obvious that one of ordinary skill in the art would recognize these concentrations are result effective variables whose ratio and concentration are a matter of routine optimization.

Also Zayzafoon et al. teach that their MSC are cultured in the RVW on beads and not without a carrier. However this would be obvious in view of Duke et al. They teach that embryonic mesenchymal cells can be either cultured on beads or without beads and can be implanted into a subject (Duke et al., pg 291 Results). Therefore since both references use RWV to culture mesenchymal cells it would be obvious to one of ordinary skill in the art to either apply the cells to beads or use no beads since Duke et al. teach that either technique is an option ((KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398 (2007) pg 12) .

Therefore claims 1-3, 5-7 and 9-11 are obvious in view of the above reference(s).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Thane Underdahl
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/Leon B Lankford/
Primary Examiner, Art Unit 1651